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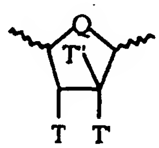
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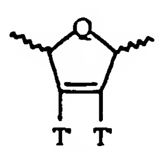
(b)

(57) Abstract: A compound having the formula (I), wherein Ar is an, optionally substituted, aromatic ring system, the aromatic ring system comprising one six-membered aromatic ring or two fused six-membered aromatic rings; R_8 and R_9 are each independently selected form the group comprising hydrogen, alkyl, cycloalkyl, halogens, amino, alkylamino, dialkylamino, nitro, cyano, alkyoxy, aryloxy, thiol, alkylthiol, arythiol, aryl; Q is selected from the group comprising O, S and CY_2, where Y may be the same or different and is selected from H, alkyl and halogens; X is selected from the group comprising O, NH, S, N-alkyl, $(CH_2)_m$ where m is 1 to 10, and CY_2 where Y may be the same or different and is selected from hydrogen, alkyl and halogens; Z is selected from the group comprising O, S, NH, and N-alkyl; U" is H and U' is selected from H and CH_2T, or U' and U" are joined so as to form a ring moiety including Q wherein U'-U" together is respectively selected from the group comprising -CTH-CT'T"- and -CT=CT- and -CT'=CT'-, so as to provide ring moieties selected from the group comprising (a), (b) wherein: T is selected from the group comprising OH, H, halogens, O-alkyl, O-acyl, O-aryl, CN, NH_2 and N_3; T' is selected from the group comprising H and halogens and, where more than one T' is present, they may be the same or different; T" is selected from the group comprising H and halogens; and W is selected from the group comprising H, a phosphate group and a pharmacologically acceptable salt, derivative or pro-drug thereof; with the proviso that when T is OAc and T' and T" are present and are H, Ar is not 4-(2-benzoxazolyl)phenyl. C_1 to C_{10} alkyl and alkoxy substituents on the aromatic ring system of Ar are preferred. Compounds show anti-viral activity, for example with respect to varicella zoster virus.

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ANTI-VIRAL PYRIMIDINE NUCLEOSIDE ANALOGUES

The present invention relates to a class of nucleoside analogues and to their therapeutic use in the prophylaxis and treatment of viral infection for example by varicella zoster virus (VZV). Varicella zoster virus is the aetiological agent in chickenpox and shingles which can cause considerable human illness and suffering.

WO 98/49177 describes a class of nucleoside analogues demonstrating anti-viral properties. A representative of the compounds disclosed in WO 98/49177 is 3-(2'-deoxy-β-D-ribofuranosyl)-6-decyl-2,3-dihydrofuro [2,3-d] pyrimidin-2-one.

"Acyclovir" is a compound known to have anti-viral properties. It is described in The Merck Index 12th Edition.

BVDU is (E)-5-(2-bromo-vinyl)-2'-deoxyuridine and is described in De Clercq *et al.* Proc. Natl. Acad. Sci.,USA 1979, 76, 2947.

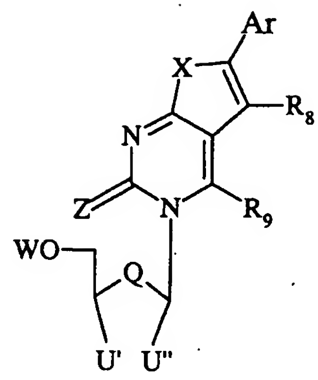
G.T. Crisp and B.L. Flynn, J. Org. Chem. 1993, 58, 6614 describes palladium catalysed couplings of terminal alkynes with a variety of oxyuridines. One coupling described is that between 5-ethynyl-2'-deoxyuridine and a range of fluorinated aryl compounds.

E. V. Malakhova *et al.* Bioorg. Khim. (1998), 24(9), 688-695 describes reagents for introducing a fluorescent deoxyuridine 2-phenylbenzoxazole derivative into oligonucleotides.

It is the object of the present invention to provide a novel class of nucleoside analogues.

It is a further object of the present invention to provide a class of nucleoside analogues for therapeutic use in the prophylaxis and treatment of a viral infection, for example a varicella zoster virus (VZV).

According to the first aspect of the present invention there is provided a compound having formula I as follows:



(I)

wherein:

Ar is an, optionally substituted, aromatic ring system, the aromatic ring system comprising one six-membered aromatic ring or two fused six-membered aromatic rings;

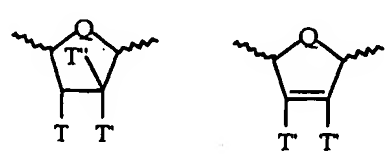
R_8 and R_9 are each independently selected from H, alkyl, aryl, cycloalkyl, halogen, amino, nitro, thiol, cyano, alkylamino, dialkylamino, alkoxy, aryloxy, alkylthiol, and arylthiol;

Q is selected from the group comprising O, S, and CY_2, where Y may be the same or different and is selected from H, alkyl, and halogen;

X is selected from the group comprising O, NH, S, N-alkyl, $(CH_2)_m$ where m is 1 to 10, and CY_2, where Y may be the same or different and is selected from H, alkyl, and halogen;

Z is selected from the group comprising O, S, NH, and N-alkyl;

U'' is H and U' is selected from H and CH_2T, or U' and U'' are joined so as to provide a ring moiety including Q wherein U'-U'' together is respectively selected from the group comprising CTH-CT'T'' and CT'=CT', so as to provide the following ring moiety options:



wherein T is selected from the group comprising OH, H, halogens, O-alkyl, O-acyl, O-aryl, CN, NH_2, and N_3;

T' is selected from the group comprising H and halogens and where more than one T' is present, they may be the same or different;

T'' is selected from the group comprising H and halogens; and

W is selected from the group comprising H, a phosphate group, and a phosphonate group;

with the proviso that when T is OAc and T' and T" are present and are H, Ar is not 4-(2-benzoxazolyl)phenyl.

It is to be understood that the present invention extends to compounds according to formula I wherein the group W is modified to provide any pharmacologically acceptable salt or derivative of H, phosphate, or phosphonate. The present invention also includes any pro-compound which is a pro-drug of the compound according to formula (I), any such pro-drug being provided by modification of the moiety W, wherein W is selected from phosphates and derivatives thereof, and phosphonates and derivatives thereof.

The aromatic ring system present in Ar may contain one, two, three or four suitable ring heteroatoms, whose position may be varied. Any ring heteroatoms present may be the same or different and can, for example, be O, S or N.

Preferably the aromatic ring system in Ar is carbocyclic. The aromatic ring system in Ar is thus preferably selected from the group comprising, optionally substituted, phenyl and naphthyl radicals. More preferably, the aromatic ring system in Ar comprises one six-membered carbocyclic ring and is thus phenyl or a substituted derivative of phenyl.

When the aromatic ring system is naphthyl or a substituted derivative of naphthyl, the naphthyl radical is preferably bonded to the nucleoside ring system at a position adjacent the fused bond in the naphthyl radical.

Preferably the aromatic ring system in Ar is substituted. Preferably the aromatic ring system in Ar is substituted by one or more moieties independently selected from the group comprising H, alkyl, aryl, and cycloalkyl, chlorine, bromine, iodine, cyano, alkylamino, dialkylamino, alkoxy, aryloxy, alkylthiol and arylthiol. Suitable moieties for use as substituents on the aromatic ring system of Ar include C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_1-C_{10} alkylamino, C_3-C_{10} dialkylamino, C_1-C_{10} alkoxy, C_6-C_{10} aryloxy, C_1-C_{10} alkylthiol, and C_6-C_{10} aryl.

Any alkyl, cycloalkyl, aryl or alkoxy substituents on the aromatic ring system of Ar may themselves be substituted. Preferably such substituents on the said alkyl, cycloalkyl, aryl and alkoxy substituents comprise one or more members independently selected from the group comprising chlorine, bromine, iodine, CN, CO_2 alkyl (C_1 to C_6), $CONH_2$, CONH alkyl (C_1 to C_6), SH, S alkyl (C_1 to C_6) and NO_2.

Preferably any substituent present in or on the aromatic ring system of Ar is at least substantially non-polar. Preferably any such substituent is hydrophobic.

Preferably any substituent or substituents on the aromatic ring system of the Ar comprise one or more alkoxy moieties and/or one or more, optionally substituted, alkyl moieties.

Any alkyl or alkoxy moiety present on the aromatic ring system of Ar is preferably straight chained, unsubstituted and saturated. Branched, substituted and/or unsaturated alkyl or alkoxy groups may however be employed. The term 'alkyl' with respect to any substituent present on the aromatic ring system thus comprises any aliphatic non-cyclic hydrocarbyl radical, including alkenyl and alkynyl. The nature, position, and number of any substituents and unsaturation may be varied.

Preferably any such alkyl or alkoxy moiety or moieties, in total, comprise 3 to 8 carbon atoms, calculated excluding any substituents that may be present on the said alkyl or alkoxy moiety or moieties. The remainder of any substituent positions on the aromatic ring system of Ar are preferably H. More preferably any alkyl moiety or moieties present on the aromatic ring system of Ar comprise, in total, from 4 to 7 carbon atoms, even more preferably from 5 to 6 carbon atoms, calculated excluding any substituents that may be present on the said alkyl moiety or moieties. More preferably any alkoxy moiety or

moieties present on the aromatic ring system of Ar comprise, in total, from 3 to 7 carbon atoms, calculated excluding any substituents that be present on the said alkoxy or alkoxy moieties.

Any alkyl moiety or moieties present on the aromatic ring system of Ar is preferably selected from the group comprising C_1, C_2, C_3, C_4, C_5, C_6, C_7 and C_8 alkyl moieties and mixtures thereof, more preferably from the group comprising C_3, C_4, C_5, C_6, C_7 and C_8 alkyl moieties and mixtures thereof, even more preferably from the group comprising C_4, C_5, C_6 and C_7 alkyl moieties and mixtures thereof. Preferably an alkyl moiety or moieties is selected from the group comprising C_5 and C_6 alkyl moieties and mixtures thereof.

Where the substituent present on the aromatic ring system is an aryl moiety, it is preferably phenyl. Such aryl substituents can be substituted. Preferably any such substituents are selected from the group set out above.

Any substituent on the aromatic ring system of Ar can be at any position. Any of the *meta*, *ortho* or *para* positions can therefore be occupied by a substituent. Preferably any single substituent, particularly where the aromatic ring system comprises a phenyl derivative, is a *para* substituent with respect to the bond between the aromatic ring system and the nucleoside fused ring system. Preferably the aromatic ring system of Ar is a six-membered carbocyclic ring system and comprises one alkyl or one alkoxy substituent at the *para* position.

Each of R_8 and R_9 may be substituted or unsubstituted, and may be branched or unbranched as appropriate to their structure. When either of R_8 and R_9 are alkyl or cycloalkyl they may be saturated or unsaturated. The nature, position, and number of any substituents and unsaturation present may be varied.

When either of R_8 and R_9 is alkyl or cycloalkyl, suitable substituents that may optionally be present include OH, halogen, amino, CN, CO_2H, CO_2 alkyl, $CONH_2$, CONH alkyl, SH, S alkyl, and NO_2, wherein alkyl in a substituent is suitably C_1-C_6. Suitably, any substituent is non-polar, more suitably any such substituent is hydrophobic.

Suitably R_8 is selected from the group comprising H, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_1-C_{10} alkylamino, C_1-C_{10} dialkylamino, C_1-C_{10} alkyloxy, C_6-C_{10} aryloxy, C_1-C_{10} alkylthiol, and C_6-C_{10} aryl.

Suitably R_9 is selected from the group H, C_1-C_{10} alkyl, C_3-C_{10} cycloalkyl, C_1-C_{10} alkylamino, C_1-C_{10} dialkylamino, C_1-C_{10} alkyloxy, C_6-C_{10} aryloxy, C_1-C_{10} alkylthiol, and C_6-C_{10}aryl.

Preferably each of R_8 and R_9 is a small alkyl, ie. a C_1-C_2 alkyl group, or H. More preferably, each of R_8 and R_9 is H.

Throughout the present specification 'halogen' is taken to include F, Cl, Br and I. Unless otherwise stated, chlorine and bromine are preferred.

Unless otherwise stated, throughout the present specification 'alkyl' is taken to include C_1-C_{10} alkyl, preferably C_1-C_5 alkyl, and saturated and unsaturated, branched and unbranched, and substituted and unsubstituted aliphatic hydrocarbyl.

Unless otherwise stated, throughout the present specification 'cycloalkyl' is taken to include C_3-C_{10}, preferably C_5-C_8, and saturated and unsaturated and substituted and unsubstituted cyclic aliphatic hydrocarbyl.

Unless otherwise stated, throughout the present specification 'aryl' is taken to include C_5-C_{10} single ring or fused bi-ring aryl, substituted and unsubstituted aryl, and aryl containing 1 to 4 heteroatoms, which may be the same or different and may be selected from, for example, O, N and S.

Suitable substituents for 'alkyl', 'cycloalkyl' and 'aryl', other than when an alkyl, cycloalkyl or aryl moiety is present as a substituent on the aromatic ring system in Ar, include one or more members independently selected from the group comprising OH, halogen, amino, CN, CO_2H, CO_2 alkyl(C_1 to C_6), $CONH_2$, CONH alkyl(C_1 to C_6), SH, S alkyl(C_1 to C_6) and NO_2.

Preferably Q is CH_2, S, or O. More preferably Q is O. Where Q is CY_2 and includes a halogen, it is preferably F. Y is preferably H.

Preferably X is O, S, or NH. More preferably X is O. Where X is $(CH)_n$, n is preferably 1 or 2, most preferably 1. Suitably, when X is N-alkyl, alkyl is C_1-C_5, and when X is CY_2, at least one Y is C_1-C_5 alkyl. Most preferably, X is O.

Preferably Z is O. Where Z is N-alkyl, suitably the alkyl is C_1-C_5.

Preferably U' and U'' are joined to provide the saturated ring moiety including T, T' and T''. Preferably T, T', and T'' in such a ring moiety are respectively OH, H, and H.

Preferably T is OH. When T is halogen it is preferably F.

Preferably each of T' and T'' is H. When either or both of T' and T'' is halogen, it is preferably F.

When W is a moiety which renders the compound a pro-drug of the compound according to Formula (I) it is to be understood that the term pro-drug includes the corresponding free base of each of the nucleosides described.

It is also to be understood that the term 'phosphate' includes diphosphates and triphosphates. Hence, W includes pharmacologically acceptable salts and derivatives of phosphates, diphosphates, and triphosphates, and of phosphonates, diphosphonates, and triphosphonates. It also includes any moiety which provides a compound which is a pro-drug of the compound according to formula (I), wherein W is selected from phosphates, diphosphates, and triphosphates, and derivatives thereof, and phosphonates, diphosphonates, and triphosphonates, and derivatives thereof.

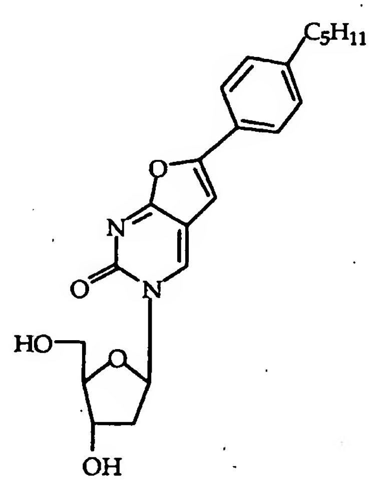
Each compound of the present invention may be a pure stereoisomer coupled at each of its chiral centres or it may be inverted at one or more of its chiral centres. It may be a single stereoisomer or a mixture of two or more stereoisomers. If it is a mixture the ratio may or may not be equimolar. Preferably the compound is a single stereoisomer. The compound may be in either enantiomeric form i.e. it may be either the D or L enantiomer either as a single stereoisomer or as a mixture of the two enantiomers. More preferably the compounds has a stereochemistry resembling natural deoxy nucleosides derived from β-D-

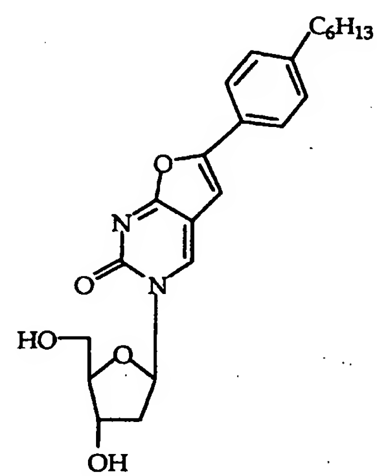
2-deoxyribose. However other enantiomers particularly the L enantiomers may be employed.

It is to be understood that the present invention extends to compounds wherein the sugar moiety and phosphate if present have either together or separately been modified as well known to a person skilled in art. For example the sugar substituent on the nucleoside may be usefully phosphonated.

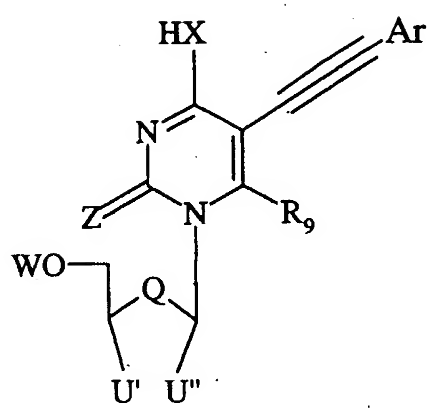
It is also possible for a compound embodying the present invention to be in a sugar form as for example modified and derived from a D-xylo sugar system.

Particularly preferred compounds embodying the present invention have the following formulae:





According to a further aspect of the present invention there is provided a method for preparing compounds having Formula I above wherein a 5-halo nucleoside analogue is contracted with a terminal alkyne in the present of a catalyst. Alternatively 5-alkynyl nucleoside can be cyclised in the presence of a catalyst. Suitably the catalyst is a copper catalyst. The 5-alkynyl nucleoside has the general formula:



Compounds embodying the present invention can show antiviral activity. In particular it has surprisingly been found that compounds embodying the present invention can show antiviral activity against for example varicella zoster virus.

According to a further aspect of the present invention there is provided a compound according to the present invention for use in a method of treatment, suitably in the prophylaxis or treatment of a viral infection.

According to a further aspect of the present invention there is provided use of a compound according to the present invention in the manufacture of a medicament for the prophylaxis or treatment of viral infection.

According to a further aspect of the present invention there is provided a method of prophylaxis or treatment of viral infection comprising administration to a patient in need of such treatment an effective dose of a compound according to the present invention

According to a further aspect of the present invention there is provided use of a compound of the present invention in the manufacture of a medicament for use in the prophylaxis or treatment of a viral infection, particularly an infection with the varicella zoster virus.

According to a further aspect of the present invention there is provided a pharmaceutical composition comprising a compound of the present invention in combination with a pharmaceutically acceptable excipient.

Medicaments embodying the present invention can be administered by oral or parenteral routes, including intravenous, intramuscular, intraperitoneal, subcutaneous, transdermal, airway (aerosol), rectal, vaginal and topical (including buccal and sublingual) administration.

For oral administration, compounds embodying the present invention will generally be provided in the form of tablets or capsules, as a powder or granules, or as an aqueous solution or suspension.

Tablets for oral use may include the active ingredient mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose, while corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin, while the lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract.

Capsules for oral use include hard gelatin capsules in which the active ingredient is mixed with a solid diluent, and soft gelatin capsules wherein the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

Formulations for rectal administration may be presented as a suppository with a suitable base comprising for example cocoa butter or a salicylate.

Formulations suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or spray formulations containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

For intramuscular, intraperitoneal, subcutaneous and intravenous use, compounds embodying the present invention will generally be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity. Suitable aqueous vehicles include Ringer's solution and isotonic sodium chloride. Aqueous suspensions embodying the invention may include suspending agents such as cellulose derivatives, sodium alginate, polyvinyl-pyrrolidone and gum tragacanth, and a wetting agent such as lecithin. Suitable preservatives for aqueous suspensions include ethyl and n-propyl p-hydroxybenzoate.

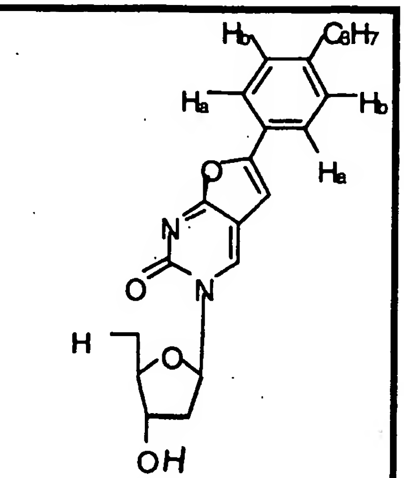
Compounds embodying the present invention can be presented as liposome formulations.

In general, a suitable dose will be in the range of 0.001 to 300 mg per kilogram body weight of the recipient per day, preferably in the range of 0.01 to 25 mg per kilogram body weight per day and most preferably in the range 0.05 to 10 mg per kilogram body weight per day. The desired dose is preferably presented as two, three, four, five or six or more sub-doses administered at appropriate intervals throughout the day. These sub-doses may be administered in unit dosage forms, for example, containing 0.1 to 1500 mg, preferably 0.2 to 1000 mg, and most preferably 0.5 to 700 mg of active ingredient per unit dosage form.

Embodiments of the present invention will now be described by way of example only.

Example 1

Preparation of 3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-n-propylphenyl)-2,3 dihydrofuro-[2,3-d]pyrimidin-2-one



$C_{20}H_{22}N_2O_5$
Exact Mass: 370.15
Mol. Wt.: 370.40
C, 64.85; H, 5.99; N, 7.56; O, 21.60

To a solution of 5-(4-n-propyl-phenylacetylene)-2'-deoxyuridine (200 mg, 0.54 mmol) in methanol and triethylamine (7:3) (20 ml), was added copper iodide (20 mg, 0.102 mmol). The mixture was refluxed for 4 hours. The solvent was removed *in vacuo*, and the crude product as purified by flash column chromatography (initial eluent : ethyl acetate, followed by : ethyl acetate / methanol (9:1)). The combined fractions were combined and the solvent was removed *in vacuo* to give the crude product, which was recrystallised from methanol to give pure 3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-n-propylphenyl)-2,3-dihydrofuro-[2,3-d]pyrimidin-2-one (86 mg, 43 %)

^{1}H-NMR (d_6-DMSO; 300 MHz); 8.72 (1H, s, **H-4**), 7.43 (2H, H_a) - 7.28 (2H, H_b) (AB system, ^3J = 7.89 Hz, ^4J = 2.3 Hz), 7.15 (1H, s, **H-5**), 6.18 (1H, dd, ^3J = 6.15 Hz, **H-1'**), 5.31 (1H, d, ^3J = 4.0 Hz, **3'-OH**), 5.12 (1H, t, ^3J = 5.01 Hz, **5'-OH**), 4.31 (1H, m, **H-3'**), 3.89 (1H, m, **H-4'**), 3.51 (2H, m, **H-5'**), 2.65 (2H, t, ^3J = 6.9 Hz, **α-CH_2**), 2.31 and 2.12 (2H, m, **2-H'a** and **2-H'b**), 1.58 (2H, sxt, **CH_2**, ^3J = 6.9 Hz), 0.85 (3H, t, ^3J = 6.9 Hz, **CH_3**).

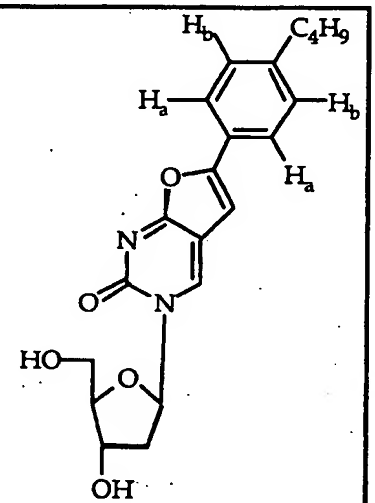
^{13}C-NMR (d_6-DMSO; 75 MHz): 13.2 (**CH_3**), 20.1, 22.3, (**C_2H_4**), 41.5 (**C-2'**), 62.3 (**C-5'**), 71.6 (**C-3'**), 83.2, 88.4 (**C-1', C-4'**), 100.4 (**C-5**), 104.6 (**C-4a**), 125.3 (**C-H_b**), 128.4 (***ipso*-C**), 131.8 (**C-H_a**), 141.2 (***para*-C**), 138.5 (**C-4**), 154.6 (**C-6**), 159.1 (**C-2**), 172.3 (**C-7a**).

General Procedure for the preparation of 3-(2'-deoxy- β -D-ribofuranosyl)-6-(4-n-alkylphenyl)-2,3-dihydrofuro-[2,3-d]pyrimidin-2-one analogues

To a stirred solution of 5-iodo-2'-deoxyuridine (800 mg, 2.26 mmol) in anhydrous dimethylformamide (8 ml), was added diisopropylethylamine (584 mg, 0.8 ml, 4.52 mmol), the 4-n-alkyl-phenylacetylene (6.76 mmol), *tetrakis*(triphenylphoshine)palladium (0) (261 mg, 0.266 mmol) and copper (I) iodide (86 mg, 0.452 mmol). The mixture was stirred for 18 hours, at room temperature, under a nitrogen atmosphere, after which time tlc (ethyl acetate / methanol 9:1), showed complete conversion of the starting material. Copper (I) iodide (80 mg, 0.40 mmol), triethylamine (15 ml) and methanol (20 ml) were then added to the mixture, which was subsequently refluxed for 4 hours. The reaction mixture was then concentrated *in vacuo*, and the resulting residue was dissolved in dichloromethane and methanol (1:1) (6 ml), whereupon an excess of Amberlite IRA-400 (HCO_3^- form) was added and stirred for 30 minutes. The resin was filtered and washed with methanol, and the combined filtrate was evaporated to dryness. The crude product was purified by flash column chromatography (Initial eluent : ethyl acetate, followed by : ethyl acetate / methanol (9:1)). The appropriate fractions were combined, where the solvent was removed *in vacuo*, to give the pure product.

Example 2

Preparation of 3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-n-butylphenyl)-2,3 dihydrofuro-[2,3-d]pyrimidin-2-one



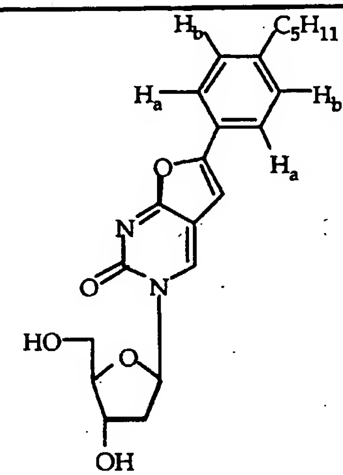
$C_{21}H_{24}N_2O_5$
Exact Mass: 384.17
Mol. Wt.: 384.43
C, 65.61; H, 6.29; N, 7.29; O, 20.81

The above general procedure was carried out using 4-n-butyl-phenylacetylene (1.072 g, 6.76 mmol), which gave 3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-n-butylphenyl)-2,3-dihydrofuro-[2,3-d]pyrimidin-2-one (140 mg, 16 %), after purification by column chromatography.

^{1}H-NMR (d_6-DMSO; 300 MHz); 8.76 (1H, s, **H-4**), 7.46 (2H, H_a) - 7.31 (2H, H_b) (AB system, ^3J = 7.89 Hz, ^4J = 2.3 Hz), 7.20 (1H, s, **H-5**), 6.21 (1H, dd, ^3J = 6.15 Hz, **H-1'**), 5.37 (1H, d, ^3J = 4.0 Hz, **3'-OH**), 5.31 (1H, t, ^3J = 5.01 Hz, **5'-OH**), 4.31 (1H, m, **H-3'**), 3.75 (1H, m, **H-4'**), 3.48 (2H, m, **H-5'**), 2.65 (2H, t, ^3J = 6.9 Hz, **α-CH$_2$**), 2.31 and 2.12 (2H, m, **2-H'a** and **2-H'b**), 1.62 (4H, m, **CH$_2$**), 0.87 (3H, t, ^3J = 6.9 Hz, **CH$_3$**). ^{13}C-NMR (d_6-DMSO; 75 MHz): 13.2 (**CH$_3$**), 20.1, 22.3, 27.9 (**C_3H_6**), 42.5 (**C-2'**), 63.7 (**C-5'**), 73.6 (**C-3'**), 83.5, 88.7 (**C-1', C-4'**), 100.8 (**C-5**), 108.4 (**C-4a**), 125.3 (**C-H$_b$**), 128.4 (***ipso*-C**), 131.8 (**C-H$_a$**), 141.2 (***para*-C**), 138.5 (**C-4**), 154.6 (**C-6**), 159.1 (**C-2**), 170.9 (**C-7a**).

Example 3

Preparation of 3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-n-pentylphenyl)-2,3-dihydrofuro-[2,3-d]pyrimidin-2-one



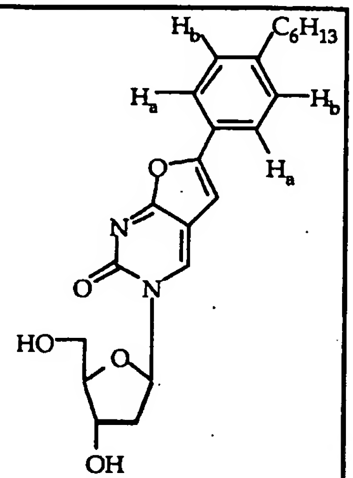
$C_{22}H_{26}N_2O_5$
Exact Mass: 398.18
Mol. Wt.: 398.46
C, 66.32; H, 6.58; N, 7.03; O, 20.08

The above general procedure was carried out using 4-n-pentyl-phenyllacetylene (1.15 g, 6.76 mmol), which gave 3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-n-pentylphenyl)-2,3-dihydrofuro-[2,3-d]pyrimidin-2-one (137 mg, 15 %), after purification by column chromatography.

^{1}H-NMR (d_6-DMSO; 300 MHz); 8.81 (1H, s, **H-4**), 7.51 (2H, **H_a**) - 7.35 (2H, **H_b**) (AB system, ^3J = 7.89 Hz, ^4J = 2.3 Hz), 7.18 (1H, s, **H-5**), 6.23 (1H, dd, ^3J = 6.15 Hz, **H-1'**), 5.37 (1H, d, ^3J = 4.0 Hz, **3'-OH**), 5.31 (1H, t, ^3J = 5.01 Hz, **5'-OH**), 4.34 (1H, m, **H-3'**), 3.79 (1H, m, **H-4'**), 3.41 (2H, m, **H-5'**), 2.67 (2H, t, ^3J = 6.9 Hz, **α-CH_2**), 2.34 and 2.14 (2H, m, **2-H'a** and **2-H'b**), 1.67 (2H, m, **CH_2**), 1.51-1.32 (4H, m, **CH_2**), 0.84 (3H, t, ^3J = 6.9 Hz, **CH_3**). ^{13}C-NMR (d_6-DMSO; 75 MHz): 13.2 (**CH_3**), 20.1, 22.3, 27.9, 28.4, (**C_4H_8**), 41.3 (**C-2'**), 62.6 (**C-5'**), 71.8 (**C-3'**), 83.4, 86.4 (**C-1', C-4'**), 100.4 (**C-5**), 107.4 (**C-4a**), 125.4 (**C-H_b**), 127.4 (*ipso*-**C**), 131.8 (**C-H_a**), 138.5 (**C-4**), 141.3 (*para*-**C**), 154.6 (**C-6**), 161.1 (**C-2**), 170.9 (**C-7a**).

Example 4

Preparation of 3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-n-hexylphenyl)-2,3 dihydrofuro-[2,3-d]pyrimidin-2-one



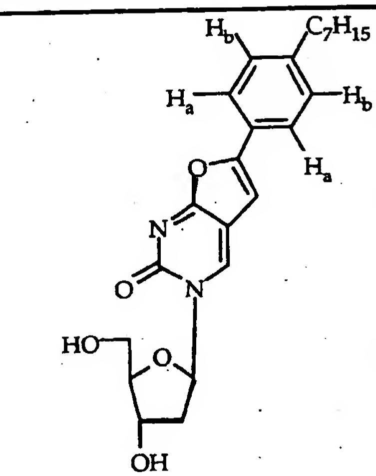
$C_{23}H_{28}N_2O_5$
Exact Mass: 412.20
Mol. Wt.: 412.48
C, 66.97; H, 6.84; N, 6.79; O, 19.39

The above general procedure was carried out using 4-n-hexyl-phenylacetylene (1.25 g, 6.76 mmol), which gave 3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-n-hexylphenyl)-2,3-dihydrofuro-[2,3-d]pyrimidin-2-one (124 mg, 13 %), after purification by column chromatography.

^{1}H-NMR (d_6-DMSO; 300 MHz); 8.85 (1H, s, **H-4**), 7.53 (2H, **H_a**) - 7.29 (2H, **H_b**) (AB system, ^3J = 7.89 Hz, ^4J = 2.3 Hz), 7.23(1H, s, **H-5**), 6.24 (1H, dd, ^3J = 6.15 Hz, **H-1'**), 5.58 (1H, d, ^3J = 4.0 Hz, **3'-OH**), 5.29 (1H, t, ^3J = 5.01 Hz, **5'-OH**), 4.54 (1H, m, **H-3'**), 3.79 (1H, m, **H-4'**), 3.51 (2H, m, **H-5'**), 2.72 (2H, t, ^3J = 6.9 Hz, **α-CH_2**), 2.31 and 2.10 (2H, m, **2-H'a** and **2-H'b**), 1.62 (2H, m, **CH_2**), 1.42-1.22 (6H, m, **CH_2**), 0.87 (3H, t, ^3J = 6.9 Hz, **CH_3**). ^{13}C-NMR (d_6-DMSO; 75 MHz): 13.2 (**CH_3**), 20.1, 22.3, 27.9, 29.5, 30.2 (**C_5H_{10}**), 41.6 (**C-2'**), 62.3 (**C-5'**), 769.8 (**C-3'**), 83.5, 88.7 (**C-1'**, **C-4'**), 99.1 (**C-5**), 107.2 (**C-4a**), 124.3 (**C-H_b**), 126.4 (***ipso*-C**), 129.3 (**C-H_a**), 138.5 (**C-4**), 141.2 (***para*-C**), 154.6 (**C-6**), 160.9 (**C-2**), 171.3 (**C-7a**).

Example 5

Preparation of 3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-n-heptylphenyl)-2,3-dihydrofuro-[2,3-d]pyrimidin-2-one



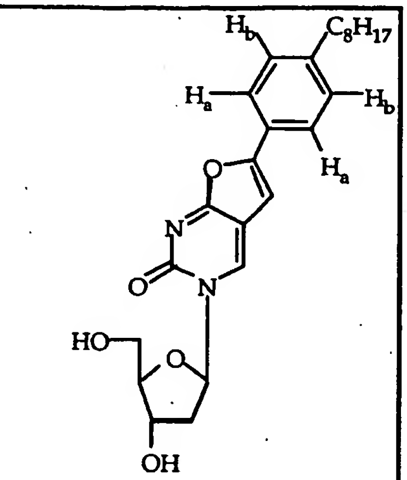
$C_{24}H_{30}N_2O_5$
Exact Mass: 426.22
Mol. Wt.: 426.51
C, 67.59; H, 7.09; N, 6.57; O, 18.76

The above general procedure was carried out using 4-n-heptyl-phenylacetylene (1.25 g, 6.76 mmol), which gave 3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-n-heptylphenyl)-2,3-dihydrofuro-[2,3-d]pyrimidin-2-one (129 mg, 13 %), after purification by column chromatography.

^{1}H-NMR (d_6-DMSO; 300 MHz); 8.91 (1H, s, **H-4**), 7.62 (2H, **H_a**) - 7.35 (2H, **H_b**) (AB system, ^3J = 7.89 Hz, ^4J = 2.3 Hz), 7.26 (1H, s, **H-5**), 6.28 (1H, dd, ^3J = 6.17 Hz, **H-1'**), 5.62 (1H, d, ^3J = 4.1 Hz, **3'-OH**), 5.32 (1H, t, ^3J = 5.12 Hz, **5'-OH**), 4.52 (1H, m, **H-3'**), 3.81 (1H, m, **H-4'**), 3.62 (2H, m, **H-5'**), 2.71 (2H, t, ^3J = 6.9 Hz, **α-CH_2**), 2.35 and 2.14 (2H, m, **2-H'a** and **2-H'b**), 1.59 (2H, m, **CH_2**), 1.48-1.21 (8H, m, **CH_2**), 0.82 (3H, t, ^3J = 6.9 Hz, **CH_3**). ^{13}C-NMR (d_6-DMSO; 75 MHz): 13.2 (**CH_3**), 20.1, 22.3, 27.9, 28.5, 29.5, 30.2 (**C_6H_{12}**), 41.6 (**C-2'**), 61.5 (**C-5'**), 69.8 (**C-3'**), 87.9, 88.5 (**C-1'**, **C-4'**), 99.1 (**C-5**), 107.2 (**C-4a**), 124.3 (**C-H_b**), 126.2 (***ipso*-C**), 129.3 (**C-H_a**), 138.2(**C-4**), 144.2 (***para*-C**), 154.6 (**C-6**), 160.7 (**C-2**), 170.6 (**C-7a**).

Example 6

Preparation of 3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-n-octylphenyl)-2,3-dihydrofuro-[2,3-d]pyrimidin-2-one



$C_{25}H_{32}N_2O_5$
Exact Mass: 440.23
Mol. Wt.: 440.54
C, 68.16; H, 7.32; N, 6.36; O, 18.16

The above general procedure was carried out using 4-n-octyl-phenylacetylene (1.45 g, 6.76 mmol), which gave 3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-n-octylphenyl)-2,3-dihydrofuro-[2,3-d]pyrimidin-2-one (111 mg, 11 %), after purification by column chromatography. ^{1}H-NMR (d_6-DMSO; 300 MHz); 8.92 (1H, s, **H-4**), 7.61 (2H, **H_a**) - 7.33 (2H, **H_b**) (AB system, ^3J = 7.89 Hz, ^4J = 2.3 Hz), 7.25 (1H, s, **H-5**), 6.21 (1H, dd, ^3J = 6.19 Hz, **H-1'**), 5.59 (1H, d, ^3J = 4.1 Hz, **3'-OH**), 5.272 (1H, t, ^3J = 5.12 Hz, **5'-OH**), 4.39 (1H, m, **H-3'**), 3.75 (1H, m, **H-4'**), 3.62 (2H, m, **H-5'**), 2.71 (2H, t, ^3J = 6.9 Hz, **α-CH_2**), 2.34 and 2.13 (2H, m, **2-H'a** and **2-H'b**), 1.61 (2H, m, **CH_2**), 1.51-1.19 (10H, m, **CH_2**), 0.82 (3H, t, ^3J = 6.9 Hz, **CH_3**). ^{13}C-NMR (d_6-DMSO; 75 MHz): 13.2 (**CH_3**), 20.1, 21.39, 22.3, 27.9, 28.5, 29.5, 30.2 (**C_7H_{14}**), 41.7 (**C-2'**), 61.1 (**C-5'**), 69.8 (**C-3'**), 87.9, 88.7 (**C-1'**, **C-4'**), 99.0 (**C-5**), 107.2 (**C-4a**), 124.8 (**C-H_b**), 126.2 (***ipso*-C**), 129.3 (**C-H_a**), 138.2(**C-4**), 144.2 (***para*-C**), 154.2 (**C-6**), 160.7 (**C-2**), 171.6 (**C-7a**).

Examples 7 to 10 and 13

The above general procedure was carried out using the appropriate starting materials to produce each of the following respective compounds:

Example 7: 3-(2'-deoxy-β-**D**-ribofuranosyl)-6-(phenyl)-2,3-dihydrofuro-[2,3-d]pyrimidin-2-one

Example 8: 3-(2'-deoxy-β-**D**-ribofuranosyl)-6-(4-methylphenyl)-2,3-dihydrofuro-[2,3-d]pyrimidin-2-one

Example 9: 3-(2'-deoxy-β-**D**-ribofuranosyl)-6-(4-ethylphenyl)-2,3-dihydrofuro-[2,3-d]pyrimidin-2-one

Example 10: 3-(2'-deoxy-β-**D**-ribofuranosyl)-6-(4-fluorophenyl)-2,3-dihydrofuro-[2,3-d]pyrimidin-2-one.

Example 13: 3-(2'-deoxy-β-**D**-ribofuranosyl)-6-(4-phenylphenyl)-2,3-dihydrofuro-[2,3-d]pyrimidin-2-one.

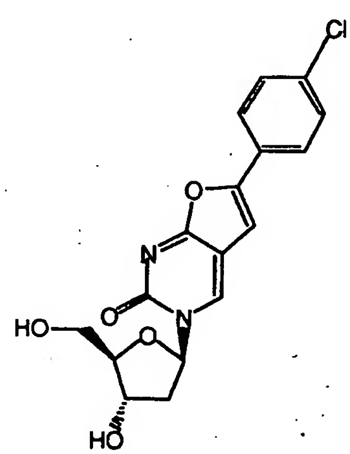
General Procedure for the preparation of 3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-n-alkoxyphenyl)-2,3-dihydrofuro-[2,3-d]pyrimidin-2-one and 3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-halophenyl)-2,3-dihydrofuro-[2,3-d]pyrimidin-2-one analogues

To a stirred solution of 5-iodo-2'-deoxyuridine (800mg, 2.26mmol) in anhydrous dimethylformamide (8ml), was added diisopropylethylamine (584mg, 0.8ml, 4.52mmol), the 4-n-alkoxy-phenylacetylene or 4-n-halo-phenylacetylene (6.76mmol), *tetrakis*(triphenylphosphine)palladium(0) (261mg, 0.266mmol) and copper (I) iodide

(86mg, 0.452mmol). The mixture was stirred for 18 hours, at room temperature, under a nitrogen atmosphere, after which time tlc (ethyl acetate / methanol 9:1), showed complete conversion of the starting material. Copper (I) iodide (80mg, 0.40mmol), triethylamine (15ml) and methanol (20ml) were then added to the mixture, which was subsequently refluxed for 4 hours. The reaction mixture was then concentrated *in vacuo*, and the resulting residue was dissolved in dichloromethane and methanol (1:1) (6ml), and an excess of Amberlite IRA-400 (HCO_3^- form) was added and stirred for 30 minutes. The resin was filtered and washed with methanol, and the combined filtrate was evaporated to dryness. The crude product was purified by flash column chromatography (initial eluent: ethyl acetate, followed by ethyl acetate / methanol (9:1). The appropriate fractions were combined and the solvent removed *in vacuo*, to give the pure product.

Example 11

3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-chlorophenyl)-2,3-dihydrofuro-[2,3-d]pyrimidin-2-one

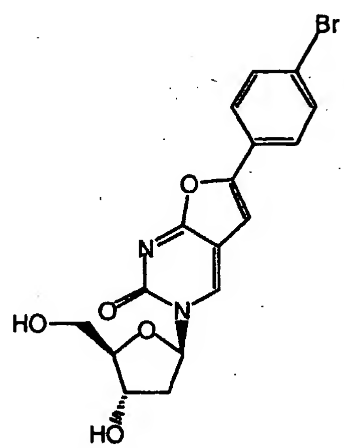


The procedure was carried out using 4-chlorophenylacetylene (0.92g, 6.76mmol), which gave 3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-chlorophenylacetylene)-2,3-dihydrofuro-[2,3-d]pyrimidin-2-one (474mg, 58%), after purification by column chromatography.

^{1}H-NMR (d_6-DMSO; 300MHz); 8.91 (1H, s, H-4), 7.88 (2H, H_a) – 7.57 (2H, H_b) (AB system, ^3J = 7.89Hz, ^4J = 2.3Hz), 7.37 (1H, s, H-5), 6.19 (1H, dd, ^3J = 6.17Hz, H1'), 5.35 (1H, d, ^3J = 4.1Hz, 3'-OH), 5.24 (1H, t, ^3J = 5.12Hz, 5'-OH), 4.26 (1H, m, H-3'), 3.95 (1H, m, H-4), 3.70 (2H, m, H-5'), 2.41 and 2.13 (2H, m, 2-H'a and 2-H'b). ^{13}CNMR (d_6-DMSO; 75MHz): 41.6 (C-2'), 60.9 (c-5'), 69.8 (C-3'), 88.0, 88.5, (C-1', C-4'), 100.8 (C-5), 107.0 (C-4a), 126.6 (C-Hb), 127.6(*ipso*-C), 129.6 (C-Ha), 134.2 (C-4), 152.8 (*para*-C), 154.1 (C-6), 161.2 (C-2), 171.8 (C-7a). MS (ES$^+$) m/e 385 (MNa$^+$, 100%), 269 (baseNa$^+$,

Example 12

3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-bromophenyl)-2,3-dihydrofuro-[2,3-d]pyrimidin-2-one



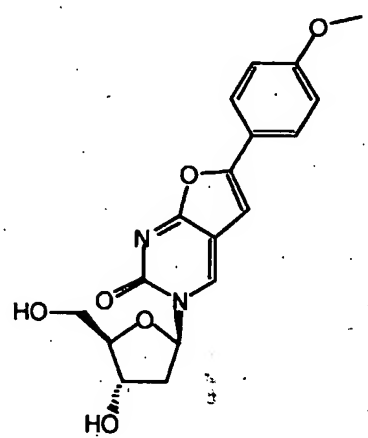
The procedure was carried out using 4-bromophenylacetylene (1.22g, 6.76mmol), which gave 3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-bromophenylacetylene)-2,3-dihydrofuro-[2,3-d]pyrimidin-2-one (174mg, 19%), after purification by column chromatography.

^{1}H-NMR (d_6-DMSO; 300MHz); 8.88 (1H, s, H-4), 7.78 (2H, H_a) – 7.66 (2H, H_b) (AB system, ^3J = 7.89Hz, ^4J = 2.3Hz), 7.34 (1H, s, H-5), 6.14 (1H, dd, ^3J = 6.17Hz, H1'), 5.31 (1H, d, ^3J = 4.1Hz, 3'-OH), 5.19 (1H, t, ^3J = 5.12Hz, 5'-OH), 4.65 (1H, m, H-3'), 3.92 (1H,

m, H-4), 3.67 (2H, m, H-5'), 2.48 and 2.19 (2H, m, 2-H'a and 2-H'b). ^{13}CNMR (d_6-DMSO; 75MHz): 41.6 (C-2'), 60.9 (c-5'), 69.8 (C-3'), 88.1, 88.5, (C-1', C-4'), 100.9 (C-5), 107.0 (C-4a), 122.9 (C-Hb), 126.8 (*ipso*-C), 127.9 (C-Ha), 139.0 (C-4), 152.8 (*para*-C), 154.1 (C-6), 160.9 (C-2), 171.3 (C-7a). MS (ES^+) m/e 429 (MNa^+, 100%), 431 (MNa^+, 100%), 313 ($baseNa^+$, 25%), 315 ($baseNa^+$, 25%). Accurate mass: $C_{17}H_{15}N_2O_5{}^{79}BrNa$ requires: 429.0062; found: 429.0061; $C_{17}H_{15}N_2O_5{}^{81}BrNa$ requires 431.0042; found: 431.0052. Found: C, 49.89%; H, 3.88%; N, 6.63%. $C_{17}H_{15}BrN_2O_5 \cdot 0.5H_2O$ requires: C, 49.04%; H, 3.88%, N, 6.73%.

Example 14

3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-methoxyphenyl)-2,3-dihydrofuro-[2,3d]pyrimidin-2-one

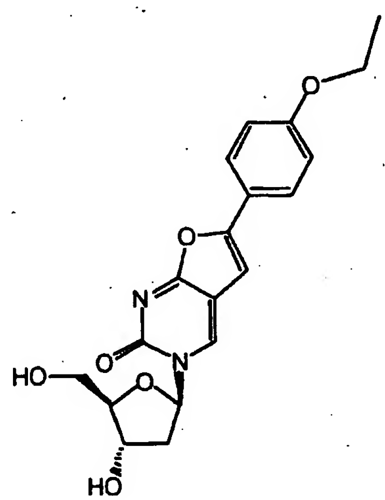


The procedure was carried out using 4-methoxyphenylacetylene (0.893g, 6.76mmol), which gave 3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-methoxyphenylacetylene)-2,3-dihydrofuro-[2,3-d]pyrimidin-2-one (353mg, 43%), after purification by column chromatography.

^{1}H-NMR (d_6-DMSO; 300MHz); 8.81 (1H, s, H-4), 7.77 (2H, H_a) – 7.12 (2H, H_b) (AB system, ^3J = 7.89Hz, ^4J = 2.3Hz), 7.06 (1H, s, H-5), 6.20 (1H, dd, ^3J = 6.17Hz, H1'), 5.32 (1H, d, ^3J = 4.1Hz, 3'-OH), 5.20 (1H, t, ^3J = 5.12Hz, 5'-OH), 4.05 (1H, m, H-3'), 3.93 (1H, m, H-4'), 3.83 (3H, s,OCH_3), 3.69 (2H, m, H-5'), 2.39 and 2.12 (2H, m, 2-H'a and 2-H'b). ^{13}CNMR (d_6-DMSO; 75MHz): 41.6 (C-2'), 55.7 (OCH_3), 61.0 (C-5'), 69.8 (C-3'), 88.5, 87.9 (C-1', C-4'), 97.7 (C-5), 107.5 (C-4a), 114.9 (C-Hb), 121.3 (*ipso*-C), 126.6 (C-Ha), 137.6 (C-4), 154.1 (*para*-C), 154.2 (C-6), 160.5 (C-2), 171.4 (C-7a). MS (ES^+) m/e 381 (MNa^+, 100%), 265 ($baseNa^+$, 20%), Accurate mass: $C_{18}H_{18}N_2O_6Na$ requires: 381.1063; found: 381.1069; Found: C, 59.83%; H, 5.29%; N, 7.83%. $C_{18}H_{18}N_2O_6$ requires: C, 60.33%; H, 5.06%, N, 7.82%.

Example 15

3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-ethoxyphenyl)-2,3-dihydrofuro-[2,3-d]pyrimidin-2-one

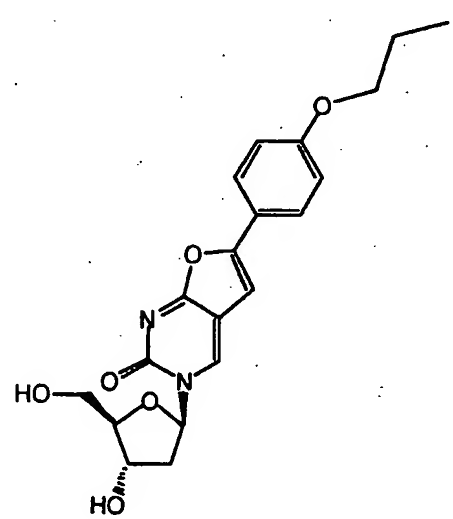


The procedure was carried out using 4-ethoxyphenylacetylene (0.988g, 6.76mmol), which gave 3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-ethoxyphenylacetylene)-2,3-dihydrofuro-[2,3-d]pyrimidin-2-one (256mg, 30%), after purification by column chromatography.

^{1}H-NMR (d_6-DMSO; 300MHz); 8.80 (1H, s, H-4), 7.77 (2H, H_a) – 7.11 (2H, H_b) (AB system, ^3J = 7.89Hz, ^4J = 2.3Hz), 7.06 (1H, s, H-5), 6.19 (1H, dd, ^3J = 6.17Hz, H1'), 5.32 (1H, d, ^3J = 4.1Hz, 3'-OH), 5.20 (1H, t, ^3J = 5.12Hz, 5'-OH), 4.26 (1H, m, H-3'), 4.08 (2H, q, OCH_2), 3.92 (1H, m, H-4), 3.69 (2H, m, H-5'), 2.40 and 2.09 (2H, m, 2-H'a and 2-H'b), 1.35 (3H, t, CH_3) ^{13}CNMR (d_6-DMSO; 75MHz): 14.9 (CH_3), 41.6 (C-2'), 61.0 (C-5'), 63.7 (OCH_2), 69.8 (C-3'), 87.9, 88.5, (C-1', C-4'), 97.6 (C-5), 107.5 (C-4a), 115.3 (C-Hb), 121.1 (*ipso*-C), 126.6 (C-Ha), 137.6 (C-4), 154.1 (*para*-C), 154.3 (C-6), 159.8 (C-2), 171.4 (C-7a). MS (ES^+) m/e 395 (MNa^+, 100%), 279 ($baseNa^+$, 20%). Accurate mass: $C_{19}H_{20}N_2O_6Na$ requires: 395.1219; found: 395.1216. Found: C, 60.97%; H, 5.67%; N, 7.29%. $C_{19}H_{20}N_2O_6$ requires: C, 61.28%; H, 5.41%, N, 7.52%

Example 16

3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-n-propoxyphenyl)-2,3-dihydrofuro-[2,3-d]pyrimidin-2-one



The procedure was carried out using 4-n-propoxyphenylacetylene (1.08g, 6.76mmol), which gave 3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-n-propoxyphenylacetylene)-2,3-

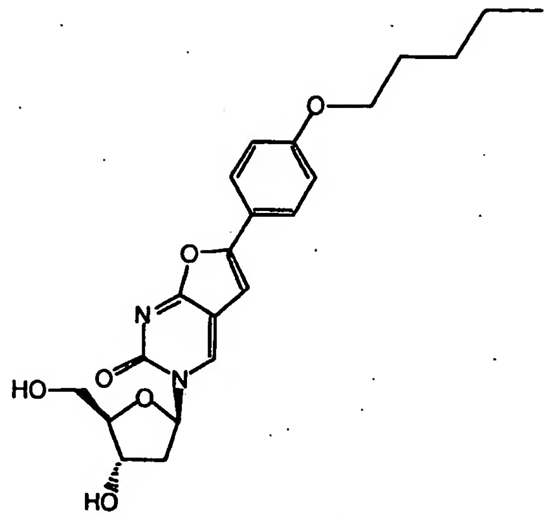
dihydrofuro-[2,3-d]pyrimidin-2-one (552mg, 59%), after purification by column chromatography.

^{1}H-NMR (d$_6$-DMSO; 300MHz); 8.80 (1H, s, H-4), 7.78 (2H, H$_a$) – 7.12 (2H, H$_b$) (AB system, ^{3}J = 7.89Hz, ^{4}J = 2.3Hz), 7.07 (1H, s, H-5), 6.19 (1H, dd, ^{3}J = 6.17Hz, H1'), 5.31 (1H, d, ^{3}J = 4.1Hz, 3

'-OH), 5.19 (1H, t, ^{3}J = 5.12Hz, 5'-OH), 4.26 (1H, m, H-3'), 4.00 (2H,t, OCH$_2$), 3.98 (1H, m, H-4'), 3.67 (2H, m, H-5'), 2.40 and 2.12 (2H, m, 2-H'a and 2-H'b), 1.80 (2H, m, CH$_2$), 1.03 (3H, t, CH$_3$) ^{13}CNMR (d$_6$-DMSO; 75MHz): 10.7 (CH$_3$), 22.3 (CH$_2$), 41.6 (C-2'), 61.0 (C-5'), 69.5 (OCH$_2$), 69.8 (C-3'), 87.9, 88.5, (C-1', C-4'), 97.6(C-5), 107.5 (C-4a), 115.4 (C-Hb), 121.1 (*ipso*-C), 126.6 (C-Ha), 137.6 (C-4), 154.1 (*para*-C), 154.3 (C-6), 160.0 (C-2), 171.3 (C-7a). MS (ES$^+$) m/e 409 (MNa$^+$, 100%), 293 (baseNa$^+$, 25%). Accurate mass: $C_{20}H_{22}N_2O_6Na$ requires: 409.1376; found: 409.1374; Found: C, 61.97%; H, 5.67%; N, 7.29%. $C_{19}H_{20}N_2O_6$ requires: C, 62.17%; H, 5.74%, N, 7.25%.

Example 17

3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-n-pentoxyphenyl)-2,3-dihydrofuro-[2,3-d]pyrimidin-2-one

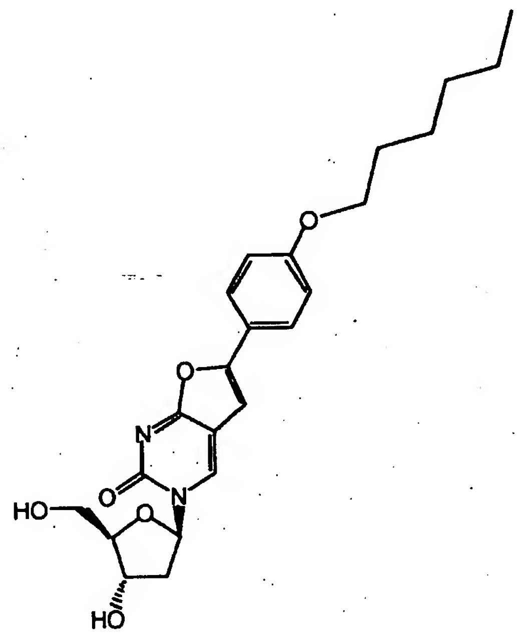


The procedure was carried out using 4-n-pentoxyphenylacetylene (1.27g, 6.76mmol), which gave 3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-n-pentoxyphenylacetylene)-2,3-dihydrofuro-[2,3-d]pyrimidin-2-one (503mg, 53%), after purification by column chromatography.

^{1}H-NMR (d_6-DMSO; 300MHz); 8.80 (1H, s, H-4), 7.78 (2H, H_a) – 7.07 (2H, H_b) (AB system, ^{3}J = 7.89Hz, ^{4}J = 2.3Hz), 7.04 (1H, s, H-5), 6.20 (1H, dd, ^{3}J = 6.17Hz, H1'), 5.31 (1H, d, ^{3}J = 4.1Hz, 3'-OH), 5.19 (1H, t, ^{3}J = 5.12Hz, 5'-OH), 4.27 (1H, m, H-3'), 4.02 (2H, t, OCH_2), 3.93 (1H, m, H-4), 3.69 (2H, m, H-5'), 2.39 and 2.13 (2H, m, 2-H'a and 2-H'b), 1.73 (2H, m, CH_2), 1.38 (4H, m, $2CH_2$), 0.91 (3H, t, CH_3). ^{13}CNMR (d_6-DMSO; 75MHz): 14.3 (CH_3), 22.2 (*C*H_2CH_3), 28.0 (*C*$H_2CH_2CH_3$), 28.6 (*C*$H_2CH_2CH_2CH_3$) 41.6 (C-2'), 61.0 (C-5'), 68.0 (OCH_2), 69.8 (C-3'), 87.9, 88.5, (C-1', C-4'), 97.6 (C-5), 107.5 (C-4a), 115.4 (C-Hb), 121.1 (*ipso*-C), 126.6 (C-Ha), 137.6 (C-4), 154.1 (*para*-C), 154.3 (C-6), 160.0 (C-2), 171.4 (C-7a). MS (ES^+) m/e 437 (MNa^+, 100%), 321 (baseNa^+, 20%). Accurate mass: $C_{22}H_{26}N_2O_6Na$ requires: 437.1689; found: 437.1695. Found: C, 60.07%; H, 6.63%; N, 6.27%. $C_{22}H_{26}N_2O_6 \cdot 1.5H_2O$ requires: C, 59.85%; H, 6.62%, N, 6.35%.

Example 18

3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-n-hexoxyphenyl)-2,3-dihydrofuro-[2,3-d]pyrimidin-2-one



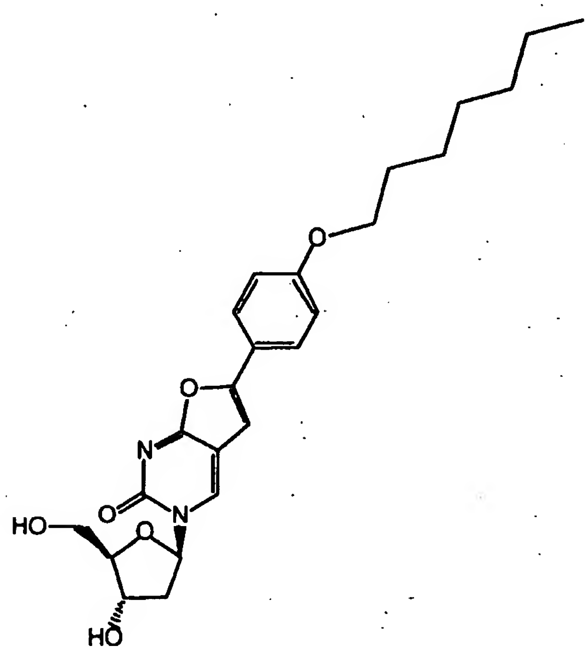
The procedure was carried out using 4-n-hexoxyphenylacetylene (1.37g, 6.76mmol), which gave 3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-n-hexoxyphenylacetylene)-2,3-dihydrofuro-[2,3-d]pyrimidin-2-one (540mg, 55%), after purification by column chromatography.

^{1}H-NMR (d_6-DMSO; 300MHz); 8.80 (1H, s, H-4), 7.77 (2H, H_a) – 7.11 (2H, H_b) (AB system, ^3J = 7.89Hz, ^4J = 2.3Hz), 7.07 (1H, s, H-5), 6.20 (1H, dd, ^3J = 6.17Hz, H1'), 5.31 (1H, d, ^3J = 4.1Hz, 3'-OH), 5.19 (1H, t, ^3J = 5.12Hz, 5'-OH), 4.26 (1H, m, H-3'), 4.02 (2H, t, OCH_2), 3.94 (1H, m, H-4), 3.70 (2H, m, H-5'), 2.41 and 2.12 (2H, m, 2-H'a and 2-H'b), 1.73 (2H, m, OCH_2CH_2), 1.43 (2H, t, $OCH_2CH_2CH_2$), 1.32 (4H, m, $2CH_2$), 0.89 (3H, t, CH_3). ^{13}CNMR (d_6-DMSO; 75MHz): 14.3 (CH_3), 22.4 (CH_2CH_3), 25.5 ($CH_2CH_2CH_3$), 28.9 ($CH_2CH_2CH_2CH_3$), 31.3 ($CH_2CH_2CH_2CH_2CH_3$), 41.6 (C-2'), 60.9 (C-5'), 68.0

(OCH_2), 69.8 (C-3'), 88.0, 88.5, (C-1', C-4'), 100.8 (C-5), 107.0 (C-4a), 115.3 (C-Hb), 121.1(*ipso*-C), 126.6 (C-Ha), 137.5 (C-4), 154.2 (*para*-C), 154.5 (C-6), 161.2 (C-2), 171.8 (C-7a). MS (ES^+) m/e 451 (MNa^+, 100%), 335 (baseNa^+, 10%). Accurate mass: $C_{23}H_{28}N_2O_6Na$ requires: 451.1845; found: 451.1843. Found: C, 64.28%; H, 6.74%; N, 6.35%. $C_{23}H_{28}N_2O_6$ requires: C, 64.47%; H, 6.59%, N, 6.54%.

Example 19

3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-n-heptoxyphenyl)-2,3-dihydrofuro-[2,3-d]pyrimidin-2-one



The procedure was carried out using 4-n-heptoxyphenylacetylene (1.46g, 6.76mmol), which gave 3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-n-heptoxyphenylacetylene)-2,3-dihydrofuro-[2,3-d]pyrimidin-2-one (193mg,19%), after purification by column chromatography.

^1H-NMR (d_6-DMSO; 300MHz); 8.80 (1H, s, H-4), 7.78 (2H, H_a) – 7.11 (2H, H_b) (AB system, ^3J = 7.89Hz, ^4J = 2.3Hz), 7.07 (1H, s, H-5), 6.20 (1H, dd, ^3J = 6.17Hz, H1'), 5.31

(1H, d, $^3J = 4.1Hz$, 3'-OH), 5.19 (1H, t, $^3J = 5.12Hz$, 5'-OH), 4.26 (1H, m, H-3'), 4.02 (2H, t, OCH_2),4.00(1H, m, H-4'), 3.92 (2H, m, H-5'), 2.51 and 2.09 (2H, m, 2-H'a and 2-H'b), 1.73 (2H, m, OCH_2CH_2), 1.33 (8H, m, $4CH_2$), 0.87 (3H, t, CH_3). 13CNMR (d_6-DMSO; 75MHz): 14.3 (CH_3), 22.4 (CH_2CH_3), 25.8 ($CH_2CH_2CH_3$), 28.8 ($CH_2CH_2CH_2CH_3$), 31.6 ($CH_2CH_2CH_2CH_2CH_3$), 33.7 ($CH_2CH_2CH_2CH_2CH_2CH_3$), 41.6 (C-2'), 61.2 (C-5'), 68.8 (OCH_2), 69.8 (C-3'), 88.1, 88.7, (C-1', C-4'), 99.7 (C-5), 107.0 (C-4a), 115.3 (C-Hb), 121.1(*ipso*-C), 126.8 (C-Ha), 137.5 (C-4), 154.2 (*para*-C), 154.5 (C-6), 161.2 (C-2), 171.8 (C-7a). MS (ES^+) m/e 465 (MNa^+, 100%), 349 (baseNa^+, 10%). Accurate mass: $C_{24}H_{30}N_2O_6Na$ requires: 465.2002; found: 465.2001. Found: C, 62.74%; H, 7.08%; N, 6.06%. $C_{24}H_{30}N_2O_6.H_2O$ requires: C, 62.59%; H, 7.01%, N, 6.08%.

10%). Accurate mass: $C_{17}H_{15}N_2O_5ClNa$ requires: 385.0567; found: 385.0575. Found: C, 56.02%; H, 4.39%; N, 7.67%. $C_{17}H_{15}ClN_2O_5$ requires: C, 56.29%; H, 4.17%, N, 7.72%.

Biological activity

The compounds of each the present examples 1 to 19 were tested *in vitro* in tissue culture assays for potent anti-viral action with respect to varicella zoster virus (VZV). The results in terms of EC_{50}, which was defined as the drug concentration (in μM) required to reduce virus-induced cytopathicity by 50%, are given in the Table below. The column titles in the table stand for:

R, for compounds embodying the present invention, is Ar as in formula I above.

EC50 VZV OKA μM stands for "50% effective concentration" and is the compound concentration required to reduce viral plaque formation after 5 days by 50%, compared to an untreated control, using OKA viral strain.

EC50 VZV YS μM stands for "50% effective concentration" and is the compound concentration required to reduce viral plaque formation after 5 days by 50%, compared to untreated control, using YS viral strain.

EC50 VZV TK $^{-}$ 07 μM stands for "50% effective concentration" and is the compound concentration required to reduce viral plaque formation after 5 days by 50%, compared to untreated control, using viral strain 07; TK deficient.

EC50 VZV TK^{-} YS μM stands for "50% effective concentration" and is the compound concentration required to reduce viral plaque formation after 5 days by 50%, compared to untreated control, using viral strain YS; TK deficient.

MCC μM is the minimum cytotoxic concentration to human embryonic lung cells.

CC50 μM is 50% cytotoxic concentration to human embryonic lung cells.

Further details of the methodology employed can be found in McGuigan *et al*. J. Med. Chem. ,1999, 42, 4479-4484.

Table

Example	R	EC50 VZV OKA μM	EC50 VZV YS μM	EC50 VZV TK- 07 μM	EC50 VZV TK- YS μM	MCC μM	CC50 μM
7	$-C_6H_5$	<0.5	<0.5	>200	162	>200	>200
8	$-pC_6H_4-CH_3$	<0.5	<0.5	103	>200	>200	>200
9	$-pC_6H_4-C_2H_5$	<0.5	<0.5	>50	>50	200	123
1	$-pC_6H_4-nC_3H_7$	0.011	0.009	>50	>20	≥50	188
2	$-pC_6H_4-nC_4H_9$	0.0032	0.0002	13	>20		
3	$-pC_6H_4-nC_5H_{11}$	0.00006	0.00005	>20	>5		
4	$-pC_6H_4-nC_6H_{13}$	0.00011	0.00007	>5	>5		
5	$-pC_6H_4-nC_7H_{15}$	0.0034	0.0009	>5	>5	5	18
6	$-pC_6H_4-nC_8H_{17}$	0.015	0.005	>20	>20	≥20	>200
Acyclovir		2.9	1	74	125	>200	>200
BVDU			0.003				
Ex2 WO 98/49177	$-nC_{10}H_{21}$	0.015	0.008	>50	>50	>50	>50
10	$-pC_6H_4-F$	>50	>50	>50	>50	200	171
11	$-pC_6H_4-Cl$	0.1	0.08	>20	>20	≥20	>200
12	$-pC_6H_4-Br$	0.29	0.2	>5	>5	>2	96
13	$-pC_6H_4-C_6H_4$	0.031	0.032	>5	>5	>200	>200
14	$-pC_6H_4-OCH_3$	0.05	0.05	>50	>50	200	>200
15	$-pC_6H_4-OC_2H_5$	0.01	0.01	50	>50	200	>200
16	$-pC_6H_4-OnC_3H_7$	0.002	0.002	11	>50	≥200	>200
17	$-pC_6H_4-OnC_5H_{11}$	0.002	0.002	3.7	>20	>50	>200
18	$-pC_6H_4-OnC_6H_{13}$	0.002	0.002	>5	>20	>20	>200
19	$-pC_6H_4-OnC_7H_{15}$	0.002	0.002	>50	>20	≥50	>200

As can be seen from the data contained in the above Table, compounds comprising Examples 2 to 5 and 15 to 19 embodying the present invention demonstrate increased

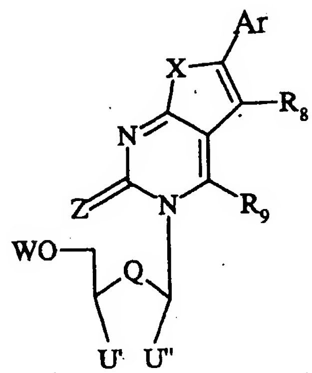
potency having regard to the known potency of the prior art compounds contained in the Table. Optimum compounds can be seen to those of Examples 2 to 5 and 16 to 19 exemplifying the present invention. Compounds displaying the greatest increase in potency can be seen to be those of Examples 3 and 4 of the present invention.

Increased potency of the compounds of the present invention permit effective reduced doses to be administered to a patient in need thereof. Reduced dosage, either in terms of the number of doses required or the quantity required per dose or both, can enhance the convenience to, and hence compliance by, the patient and can permit a commensurate reduction in likely host toxicity and any side effects.

Compounds comprising Examples 1, 6 and 11 to 14 demonstrate comparable potency having regard to the known potency of the prior art compounds contained in the Table.

CLAIMS

1. A compound having the formula:



(I)

wherein

Ar is an, optionally substituted, aromatic ring system, the aromatic ring system comprising one six-membered aromatic ring or two fused six-membered aromatic rings;

R_8 and R_9 are each independently selected from the group comprising hydrogen, alkyl, cycloalkyl, halogens, amino, alkylamino, dialkylamino, nitro, cyano, alkyoxy, aryloxy, thiol, alkylthiol, arythiol, aryl;

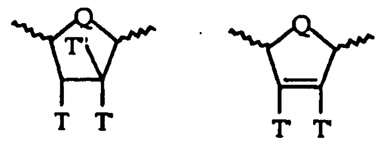
Q is selected from the group comprising O, S and CY_2, where Y may be the same or different and is selected from H, alkyl and halogens;

X is selected from the group comprising O, NH, S, N-alkyl, $(CH_2)_m$ where m is 1 to 10, and CY_2 where Y may be the same or different and is selected from hydrogen, alkyl and halogens;

Z is selected from the group comprising O, S, NH, and N-alkyl;

U" is H and U' is selected from H and CH_2T, or U' and U" are joined so as to form a ring moiety including Q wherein U'-U" together is respectively selected from the group

comprising –CTH-CT'T"-and –CT=CT-and -CT'=CT'-, so as to provide ring moieties selected from the group comprising:



wherein:

T is selected from the group comprising OH, H, halogens, O-alkyl, O-acyl, O-aryl, CN, NH_2 and N_3;

T' is selected from the group comprising H and halogens and, where more than one T' is present, they may be the same or different;

T" is selected from the group comprising H and halogens; and

W is selected from the group comprising H, a phosphate group and a pharmacologically acceptable salt, derivative or pro-drug thereof;

with the proviso that when T is OAc and T' and T" are present and are H, Ar is not 4-(2-benzoxazolyl)phenyl.

2. A compound according to claim 1 wherein the aromatic ring system in Ar contains one, two, three or four hetero ring atoms.

3. A compound according to claim 1 wherein the aromatic ring system in Ar comprises one six-membered carbocyclic ring.

4. A compound according to any one of the preceding claims wherein Ar comprises an aromatic ring system substituted by one or more moieties independently selected from the group comprising H, alkyl, aryl, cycloalkyl, chlorine, bromine, iodine, cyano, alkylamino, dialkylamino, alkoxy, aryloxy, alkylthiol and arylthiol, any alkyl, cycloalkyl

or aryl groups of which may be substituted by one or more members selected from the group comprising chlorine, bromine, iodine, CN, CO_2alkyl (C_1 to C_6), $CONH_2$, CONH alkyl (C_1 to C_6), SH, S alkyl (C_1 to C_6) and NO_2.

5. A compound according to claim 4 wherein the moiety or moieties substituted on the said aromatic ring system comprise one or more, optionally substituted, alkyl or alkoxy moieties wherein the said alkyl or alkoxy moiety or moieties, in total, comprise from 3 to 8 carbon atoms, calculated excluding any substituents that may be present on the said alkyl or alkoxy moiety or moieties.

6. A compound according to claim 5 wherein the said alkyl or alkoxy moiety or moieties comprise one or more straight chain, saturated alkyl or alkoxy moieties.

7. A compound according to claim 5 or claim 6 wherein the said alkyl or alkoxy moiety or moieties comprise, in total, one or more non-substituted alkyl or alkoxy moieties.

8. A compound according to any one of claims 5 to 7 wherein the said alkyl moiety or moieties comprise, in total, from 4 to 7 carbon atoms, calculated excluding any substituents that may be present on the said alkyl moiety or moieties .

9. A compound according to claim 8 wherein the said alkyl moiety or moieties comprise, in total, from 5 to 6 carbon atoms, calculated excluding any substituents that may be present on the said alkyl moiety or moieties.

10. A compound according to any one of claims 5 to 9 wherein the said alkyl moiety or moieties is selected from the group comprising C_1, C_2, C_3, C_4, C_5, C_6, C_7 and C_8 alkyl moieties and mixtures thereof, preferably from the group comprising C_3, C_4, C_5, C_6, C_7 and C_8 alkyl moieties and mixtures thereof, and more preferably from the group comprising C_4, C_5, C_6 and C_7 alkyl moieties and mixtures thereof.

11. A compound according to Claim 10 wherein the said alkyl moiety or moieties is selected from the group comprising C_5 and C_6 alkyl moieties and mixtures thereof.

12. A compound according to any one of claims 5 to 7 wherein the said alkoxy moiety or moieties comprise, in total, from 3 to 7 carbon atoms, calculated excluding any substituents that may be present on the said alkoxy moiety or moieties.

13. A compound according to any one of claims 5 to 12 wherein the said alkyl or alkoxy moiety comprises one alkyl or one alkoxy moiety.

14. A compound according to any one of the preceding claims wherein the aromatic ring system comprises one six-membered aromatic ring, preferably a carbocyclic aromatic ring, and one substituent, preferably one alkyl or one alkoxy moiety, at the *para* position on the six-membered aromatic ring.

15. A compound according to Claim 1 selected from the group comprising:

3-(2'-deoxy-β-**D**-ribofuranosyl)-6-(4-methylphenyl)-2,3-dihydrofuro-[2,3-*d*]pyrimidin-2-one;

3-(2'-deoxy-β-**D**-ribofuranosyl)-6-(4-ethylphenyl)-2,3-dihydrofuro-[2,3-*d*]pyrimidin-2-one;

3-(2'-deoxy-β-**D**-ribofuranosyl)-6-(4-n-propylphenyl)-2,3-dihydrofuro-[2,3-*d*]pyrimidin-2-one;

3-(2'-deoxy-β-**D**-ribofuranosyl)-6-(4-n-butylphenyl)-2,3-dihydrofuro-[2,3-*d*]pyrimidin-2-one;

3-(2'-deoxy-β-**D**-ribofuranosyl)-6-(4-n-pentylphenyl)-2,3-dihydrofuro-[2,3-*d*]pyrimidin-2-one;

3-(2'-deoxy-β-**D**-ribofuranosyl)-6-(4-n-hexylphenyl)-2,3-dihydrofuro-[2,3-*d*]pyrimidin-2-one;

3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-n-heptylphenyl)-2,3-dihydrofuro-[2,3-*d*]pyrimidin-2-one;

3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-n-octylphenyl)-2,3-dihydrofuro-[2,3-*d*]pyrimidin-2-one;

3-(2'-deoxy-β-D-ribofuranosyl)-6-(phenyl)-2,3-dihydrofuro-[2,3-*d*]pyrimidin-2-one;

3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-fluorophenyl)-2,3-dihydrofuro-[2,3-*d*]pyrimidin-2-one;

3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-chlorophenyl)-2,3-dihydrofuro-[2,3-*d*]pyrimidin-2-one;

3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-bromophenyl)-2,3-dihydrofuro-[2,3-*d*]pyrimidin-2-one;

3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-phenylphenyl)-2,3-dihydrofuro-[2,3-*d*]pyrimidin-2-one;

3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-methoxyphenyl)-2,3-dihydrofuro-[2,3-*d*]pyrimidin-2-one;

3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-ethoxyphenyl)-2,3-dihydrofuro-[2,3-*d*]pyrimidin-2-one;

3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-n-propoxyphenyl)-2,3-dihydrofuro-[2,3-*d*]pyrimidin-2-one;

3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-n-pentoxyphenyl)-2,3-dihydrofuro-[2,3-d]pyrimidin-2-one;

3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-n-hexoxyphenyl)-2,3-dihydrofuro-[2,3-d]pyrimidin-2-one;

3-(2'-deoxy-β-D-ribofuranosyl)-6-(4-n-heptoxyphenyl)-2,3-dihydrofuro-[2,3-d]pyrimidin-2-one; and

mixtures thereof.

16. A method for preparing compounds according to any one of claims 1 to 15 wherein a 5-halo nucleoside analogue is contacted with a terminal alkyne in the presence of a catalyst, or a 5-alkynyl nucleoside is cyclised in the presence of a catalyst.

17. A compound according to any one of claims 1 to 15 for use in a method of treatment.

18. Use of a compound according to any one of claims 1 to 15 in the manufacture of a medicament for the prophylaxis or treatment of a viral infection.

19. A method of prophylaxis or treatment of a viral infection comprising administering to a patient in need of such treatment an effective dose of a compound according to any claims 1 to 15.

20. A compound according to any one of claims 1 to 15 in the manufacture of a medicament for use in the prophylaxis or treatment of a viral infection.

21. A pharmaceutical composition comprising a compound according to any one of claims 1 to 15 in combination with a pharmaceutically acceptable excipient.

22. A method of preparing a pharmaceutical composition comprising the step of combining a compound according to any one of claims 1 to 15 with a pharmaceutically acceptable excipient.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 01/01694

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07H19/04 C07H19/06 A61K31/70 C07D307/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07H A61K C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CRISP G T ET AL: "PALLADIUM-CATALYZED COUPLING OF TERMINAL ALKYNES WITH 5(TRIFLUOROMETHANESULFONYLOXY) PYRIMIDINE NUCLEOSIDES" JOURNAL OF ORGANIC CHEMISTRY, AMERICAN CHEMICAL SOCIETY. EASTON, US, vol. 58, no. 24, 1993, pages 6614-6619, XP002069922 ISSN: 0022-3263 cited in the application * cpds 2-8 of Table II, page 6616 * * cpds 5 and 7 of Table III, page 6616 *	1,15,16
Y	page 6614, right-hand column, line 7-26	1-22

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"P" document published prior to the international filing date but later than the priority date claimed

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
12 September 2001	26/09/2001

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Gohlke, P

Form PCT/ISA/210 (second sheet) (July 1992)

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